

**This Page Is Inserted by IFW Operations
and is not a part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- **BLACK BORDERS**
- **TEXT CUT OFF AT TOP, BOTTOM OR SIDES**
- **FADED TEXT**
- **ILLEGIBLE TEXT**
- **SKEWED/SLANTED IMAGES**
- **COLORED PHOTOS**
- **BLACK OR VERY BLACK AND WHITE DARK PHOTOS**
- **GRAY SCALE DOCUMENTS**

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

THIS PAGE BLANK (USPTO)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
7 September 2001 (07.09.2001)

PCT

(10) International Publication Number
WO 01/64274 A2

(51) International Patent Classification⁷: A61M 15/00

(21) International Application Number: PCT/EP01/02213

(22) International Filing Date: 28 February 2001 (28.02.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0004794.4 1 March 2000 (01.03.2000) GB
0018674.2 28 July 2000 (28.07.2000) GB
0018684.1 28 July 2000 (28.07.2000) GB

(71) Applicant (for all designated States except US): **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB)

(72) Inventor; and

(75) Inventor/Applicant (for US only): **HAILEY, Mark, Andrew** [GB/GB]; Glaxo Wellcome plc, Park Road, Ware, Hertfordshire SG12 0DJ (GB).

(74) Agent: **CRAWLEY, Karen**; GlaxoSmithKline, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette

(54) Title: **METERED DOSE INHALER**

(57) Abstract: There is provided according to the invention a metered dose inhaler comprising an interfacial surface having a linear

WO 01/64274 A2

METERED DOSE INHALER

The present invention relates to metered dose inhalers. More especially, the invention relates to a metered dose inhaler for consistently dispensing a prescribed dose of medicament.

Drugs for treating respiratory and nasal disorders are frequently administered in aerosol formulations through the mouth or nose. One widely used method for dispensing such aerosol drug formulations involves formulating the drug as a suspension or a solution in a liquefied gas propellant. The suspension/solution is stored in a sealed canister capable of withstanding the pressure required to maintain the propellant as a liquid. The suspension/solution is dispersed by activation of a dose metering valve affixed to the canister.

A metering valve generally comprises a metering chamber which is of a set volume and is designed to administer per actuation an accurate predetermined dose of medicament. As the suspension is forced from the canister through the dose metering valve by the high vapour pressure of the propellant, the propellant rapidly vaporizes leaving a fast moving cloud of very fine particles of the drug formulation. This cloud of particles is directed into the nose or mouth of the patient by a channeling device such as a cylinder or open-ended cone. Concurrently with the activation of the aerosol dose metering valve, the patient inhales the drug particles into the lungs or nasal cavity. Systems of dispensing drugs in this way are known as "metered dose inhalers" (MDI's). See Peter Byron, Respiratory Drug Delivery, CRC Press, Boca Raton, FL (1990) for a general background on this form of therapy.

Patients often rely on medication delivered by MDI's for rapid treatment of respiratory disorders which are debilitating and in some cases even life threatening. Therefore, it is essential that the prescribed dose of aerosol medication delivered to the patient consistently meet the specifications claimed by the manufacturer and comply with the requirements of the FDA and other regulatory authorities. That is, every dose dispensed from the can must be the same within close tolerances.

A problem which can exist with drug delivery devices such as MDI's is the deposition of the medicament, or the solid component from a suspension of a particulate product in a liquid propellant, onto the internal surfaces of the device which occurs after a number of operation cycles and/or storage. This can lead to a reduction in the efficacy of the device and of the
5 resulting treatment as the deposition of the product reduces the amount of active drug available to be dispensed to the patient and markedly reduces the uniformity of the dose dispensed during the lifetime of the device.

The problem of drug adherence and dose uniformity can be greater with hydrofluoroalkane
10 propellants, for example, 1,1,1,2-tetrafluoroethane (HFA134a) and 1,1,1,2,3,3,3-n-heptafluoropropane (HFA227) which have been developed as ozone friendly replacements of chlorofluorocarbons such as P11, P114 and P12.

Some prior art devices rely on the dispenser being shaken so as to agitate the liquid
15 propellant and product mixture therein, in an attempt to dislodge the deposited particles. However, while in some cases this remedy can be effective within the body of the drug container itself, it may not be effective for particles deposited on the inner surfaces of other MDI components such as the metering valve.

20 UK patent application GB-A-2,238,932 discloses the use of a liner of a material such as fluoropolymer, ceramic or glass to line a portion of the wall of the metering chamber in a metering valve of an MDI. Although this alleviates the problem of deposition in these types of dispensers, it does require the re-design or modification of mouldings and mould tools for producing the valve members to allow for insertion of the liner.

25

Canadian patent application 2130867 describes a metered dose inhaler containing an aerosol formulation in which the internal walls of the canister are coated with a cross-linked plastics coating. Polytetrafluoroethylene (PTFE) and perfluoroethylenepropylene (FEP) are specifically mentioned as suitable coating materials. International patent application
30 PCT/US96/05005 (WO96/32150) describes a metered dose inhaler in which part or all of the internal surfaces of the canister are coated with a cross-linked polymeric composition, particularly polymer blends comprising one or more fluorocarbon polymers in combination with one or more non-fluorocarbon polymers.

Whilst the aforementioned polymer coatings minimize deposition of the drug onto the walls of the canister or other MDI components, certain technical disadvantages are associated with this approach. For example, the component may deform as a result of being subject to the elevated temperatures, typically in excess of 300°C, required for the coating process.

5 Therefore, components have to be formed from thicker sheets of material which increases costs and the quantity of waste material. Furthermore, difficulties arise in ensuring adhesion of the polymer to the component walls and more particularly with uniformity of the coating over the component surface.

10 Perhaps most importantly, it has been found that the use of such polymer coatings can under certain circumstances lead to a variation in the uniformity of dose from first use through to the emptying of the MDI device.

Unexpectedly, the present inventors have found that by treating the components as
15 described herein, the need to apply a cross-linked polymer coating, and therefore the disadvantages associated therewith, is obviated. MDI's so treated advantageously reduce drug deposition onto the walls of the components and afford greater dose uniformity over the lifetime of the device.

20 Accordingly, in one aspect the invention provides a metered dose inhaler comprising an interfacial surface having a linear, non-cross-linked polymeric compound disposed thereon.

In another aspect, the invention provides a component or accessory for use in a metered dose inhaler, comprising an interfacial surface having a linear, non-cross-linked polymeric
25 compound disposed thereon.

As used herein, the term "interfacial surface" defines all or part of any internal surface of the metered dose inhaler, component or accessory, that contacts or comes into contact, i.e. forms an interface with, a medicament during storage and/or dispensing thereof.

30

As used herein, the term "metered dose inhaler" or "MDI" means a unit comprising a canister, a cap covering the mouth of the canister, a drug metering valve situated in the cap, a metering chamber and a suitable channeling device into which the canister is fitted. The

term "drug metering valve" or "MDI valve" refers to a valve and its associated mechanisms which delivers a predetermined amount of drug formulation from an MDI upon each activation. The channeling device may comprise, for example, an actuating device for the valve and a cylindrical or cone-like passage through which medicament may be delivered
5 from the filled MDI can via the MDI valve to the nose or mouth of a patient, e.g. a mouthpiece actuator. The relation of the parts of a typical MDI is illustrated in US Patent 5,261,538.

Therefore, the component or accessory may include a canister, and/or a metering valve,
10 and/or a metering chamber, and/or a channeling device and/or an actuator for use in a metered dose inhaler.

The linear, non-cross-linked polymeric compound may be disposed as a multi-molecular layer, which may be applied separately wherein the layers need not be the same compound.
15 More preferably, the linear, non-cross-linked polymeric compound is disposed as a mono-molecular layer.

The products treated according to the present invention reduce the variation in dosage with respect to a conventional cross-linked polymer coated metered dose inhaler.
20

Preferably, the metered dose inhaler is suitable for consistently dispensing a dose of medicament ranging between 90% and 110% of a prescribed single dosage. Typically, the metered dose inhaler is suitable for dispensing a dose of medicament ranging between 95% and 105% of a prescribed single dosage, for example, 97% and 103%, e.g. 98% and 102%
25

Mean dose is calculated by taking ten metered dose inhalers. The beginning of use (BOU) dose and the end of use (EOU) dose is measured for each of the ten inhalers. The mean of the 20 measurements is then calculated. The dosing consistency is calculated by looking at the dose from BOU to EOU and quoting the mean result from each of the 10 determinations
30 as a percentage of the overall mean.

As used herein, "consistently dispensing" defines the dose uniformity of the aerosol medication dispensed to the patient from the first dose through to the final dose dispensed from a drug canister in the MDI device.

- 5 Preferably, the linear, non-cross-linked polymeric compound is a fluorocarbon. More preferably, the compound is highly fluorinated, i.e. has a high ratio of fluorine to carbon.

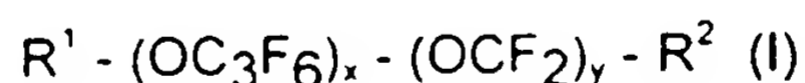
The polymeric compounds will generally be employed as mixtures, the nature of which may be varied as part of optimisation of the employment of the invention.

10

Typically, the linear, non-cross-linked polymeric compound comprises a functional grouping which is capable of anchoring the compound to the surface of the substrate (e.g. component).

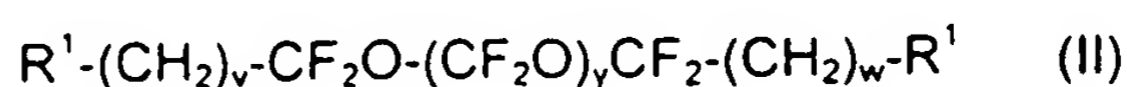
- 15 In a first preferred embodiment, the compound is an organo-phosphate, for example, a phosphate-based perfluoroether derivative. Typically, the compound may take the form of a phosphoric ester.

- In one first such embodiment, the invention provides a metered dose inhaler, component or
20 accessory as described above, comprising an interfacial surface having a compound disposed thereon having the general formula (I):



- 25 wherein R^1 comprises a fluoro-alkyl functional group;
x and y are such that the molecular weight of the compound is 350-1000; and
 R^2 comprises a phosphate ester functional group;

- In a second such embodiment, the invention provides a metered dose inhaler, component or
30 accessory as described above, comprising an interfacial surface having a compound disposed thereon having the general formula (II):



wherein R^1 comprises:

$-(OCH_2-CH_2)_z-OPO(OH)_2$, wherein x , y and z are such that the molecular weight of the compound is 900-2100 and v and w independently represent 1 or 2.

5

In one preferred embodiment, v and w are both 1. In a second preferred embodiment v and w are both 2.

Alternatively in a second preferred embodiment, the compound is an organo-silane derivative. Typically, the compound may take the form of a silane derivative of perfluoropolyoxyalkane, especially a silane derivative of perfluoropolyoxyalkane having a molecular weight in the range 1600-1750. Examples include perfluoropolyethers having functional groups of the type $-CONR^2R^3$ wherein R^2 and R^3 may be independently selected from hydrogen, or a silyl ether (e.g. $SiR_t(OR)_{3-t}$ wherein R = hydrogen or C_{1-8} and $t=0$ to 2) as disclosed in US Patent 4 746 550 which is incorporated herein by reference.

10
15

The synthesis of compounds of formula (I) and (II) and processes for their preparation may readily be determined by reference to which describe EP 687 533 (I) and (II) similar compounds. EP 338 531 also provides information on the preparation of compounds of this type. Methods of preparing other polymeric compounds of the type described above may readily be determined by reference the aforementioned USP 4 746 550.

20

Whilst not being wishing to be bound by any theory, it is believed that the phosphate or silane moiety of the compounds as described above reacts with the surface of the component to anchor the compound to the surface. Thus, when in use, the per-fluorinated end of the compound is presented to the pharmaceutical formulation and so provides a highly fluorinated surface.

25

Preferably, the contact angle of the interfacial surface is greater than 70 degrees, for example greater than 90 degrees, e.g. greater than 110 degrees.

30

As used herein, "contact angle" is identified as the angle between a liquid water droplet and a solid surface at the liquid/solid gas interface.

Typically, the conductivity of the interfacial surface is greater than 2.4mS, for example, greater than 4.0mS. Preferably, the conductivity is greater than 7.9mS.

As used herein, "conductivity" is evaluated by applying a low voltage of 6.3V between the interfacial surface and a salt (e.g. 1% sodium chloride) solution alongside the surface, using a WACO™ Enamel Rater II Balance, i.e. using the WACO Conductivity Test for the Determination of Coating Integrity of Metered Dose Inhalers. Therefore, measurements of the product according to this apparatus are greater than 15mA, typically greater than 25mA, e.g. greater than 50mA, which corresponds to a conductivity of greater than 2.4mS, 4.0mS and 7.9mS respectively.

The interfacial surface may be a metallic, metal alloy or plastics surface. Preferably, the interfacial surface is a metallic or metal alloy surface.

In a first preferred embodiment, the component or accessory having an interfacial surface according to the invention is a canister. In a second preferred embodiment the component or accessory having an interfacial surface according to the invention is a metering valve, especially a metering chamber.

The metered dose inhaler or a component or accessory may be suitable for storing and/or dispensing a medicament, and deposition of the medicament on the MDI, component or accessory may be reduced by between 30% and 80%, for example, between 40% and 80%, e.g. between 40% and 60%, such as about 50%.

As used herein, the reference to the reduction in deposition of medicament is with respect to the deposition that would occur on a metered dose inhaler, component or accessory which does not comprise an interfacial surface having a linear, non-cross-linked polymeric compound disposed thereon.

In a further aspect, there is provided a canister for use in a metered dose inhaler as defined above, containing a pharmaceutical aerosol formulation comprising a medicament and a fluorocarbon propellant.

Aerosol formulations which are generally used comprise a solution/suspension of medicament, one or more liquid propellants, optionally with co-propellants and optionally an adjuvant or a surfactant, though the invention may be applicable to the dispensing of any aerosol formulation.

In another aspect of the invention there is provided a metered dose inhaler comprising a canister, and/or a metering valve, and/or a metering chamber, and/or a channeling device and/or an actuator as described above.

In still another aspect, the invention provides the use of a metered dose inhaler, component or accessory as described above, for dispensing a pharmaceutical aerosol formulation comprising a medicament and a fluorocarbon propellant.

In yet a further aspect, the invention provides a process for obtaining a metered dose inhaler as defined above, comprising the treatment of the interfacial surface with a linear, non-cross-linked polymeric compound.

In another aspect, the invention provides a process for obtaining a component or accessory for use in a metered dose inhaler as described above, comprising the treatment of the interfacial surface with a linear, non-cross-linked polymeric compound.

Preferably, the interfacial surface is treated to form a multi-molecular layer thereon, which may be applied as separate layers wherein the layer need not be of the same compound. More preferably, the interfacial surface is treated to form a mono-molecular layer thereon.

In a preferred embodiment, the polymeric compound is a fluorocarbon. Typically, the compound is highly fluorinated.

Typically, the linear, non-cross-linked polymeric compound may comprise a functional grouping which is capable of anchoring the compound to the surface to be treated.

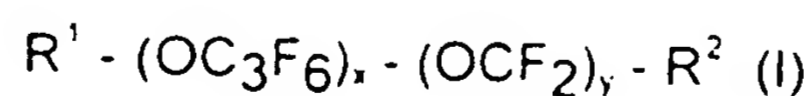
In a first preferred embodiment, the compound is an organo-phosphate, for example, a phosphate based perfluoroether derivative. Typically, the compound may take the form of a phosphoric ester. In a second equally preferred embodiment, the compound is an organo-silane derivative. Typically the compound may take the form of a silane derivative of
 5 perfluoropolyoxyalkane.

The inventors have found that such treatment of MDIs or one or more components thereof results in improved uniformity of the dose dispensed with dose number through to the emptying of the drug canister. Advantageously, unlike the use of polymer linings or
 10 coatings, the present process does not require the re-design or modification of mouldings and mould tools for producing the valve members to allow for insertion of a liner, or the need to use thick component walls in order to avoid deformation as a result of being subject to elevated temperatures, typically in excess of 300°C, which are required for the coating process. Therefore, components may now be formed from thinner sheets of material which
 15 reduces costs and the quantity of waste material. Low temperature treatment also reduces process costs.

Furthermore, difficulties arising in ensuring adhesion of a polymer to the component walls and more particularly with uniformity of the coating over the component surface are
 20 obviated.

Preferably, the process for obtaining a metered dose inhaler, component or accessory as defined above, comprises the treatment of the interfacial surface with a compound;

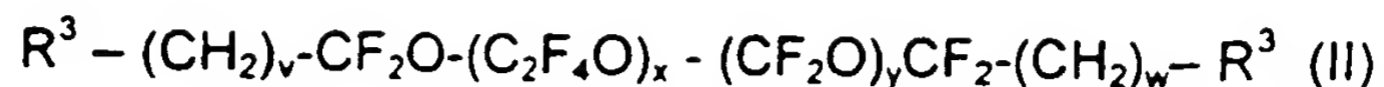
25 i) having the general formula (I)



wherein R^1 comprises a fluoro-alkyl functional group,

30 x and y are such that the molecular weight of the compound is 350-1000; and
 R^2 comprises a phosphate ester functional group; or

ii) having a general formula (II)



wherein R^3 comprises $-(OCH_2-CH_2)_z-OPO(OH)_2$;

- 5 x, y and z are such that the molecular weight of the compound is 900-2100; and
v and w independently represent 1 or 2; or

- 10 iii) a silane derivative of perfluoropolyoxyalkane with a molecular weight in the range
1600-1750.

The inventors also contemplate that the manufacturing machinery used to produce MDI's, their components and accessories may also be treated in accordance with the invention. Furthermore, apparatus for filling empty canisters, or other MDI components, with medicament may also be treated. In this way, inaccuracies due to deposition or through
15 drug metering may be prevented at the stage of loading the MDI with its full load of medicament.

The metered dose inhalers may be prepared by methods of the art (e.g. see Byron above and US patent 5,345,980) subsisting conventional cans for those treated in accordance with
20 the present invention.

Conventionally, the canisters and caps for use in MDI's are made of aluminium or an alloy of aluminium although other metals not affected by the drug formulation, such as stainless steel, an alloy of copper, or tin plate, may be used. An MDI canister may also be fabricated
25 from glass or plastic. Preferably, however, the MDI canisters and caps employed in the present invention are made of aluminium or an alloy thereof.

The drug metering valve may consist of parts usually made of stainless steel, a pharmacologically resilient polymer, such as acetal, polyamide (e.g. Nylon^R), polycarbonate, polyester, fluorocarbon polymer (e.g. Teflon^R) or a combination of these materials.
30 Additionally, seals and "O" rings of various materials (e.g., nitrile rubbers, polyurethane, acetyl resin, fluorocarbon polymers), or other elastomeric materials are employed in and around the valve.

The components of the MDI described hereinabove may be pretreated as coil stock, such as aluminium or stainless steel, before being stamped or drawn into shape. This method is well suited to high volume production due to the high standards of uniformity that can be achieved and to the high speed and precision with which pre-coated stock can be drawn or stamped.

Alternatively, the components may be manufactured according to a second process comprising treating pre-formed canisters.

Preferably, the components or coil stock are dipped or bath immersed into a treatment tank containing a solution of a polymeric compound as described above or a mixture thereof.

The components or coil stock may be treated with 0.1 to 10% w/w, preferably 0.5 to 5%, especially about 1%, solution of a polymeric compound as described above or mixture thereof in any suitable solvent such as isopropyl alcohol.

Conventional metal coating techniques such as spraying and immersion may be used to apply the treatment solution to the pre-formed components or coil stock. Preferably, the pre-formed components or the coil stock are immersed in the solution at room temperature for at least one hour, for example, 12 hours, thus being treated both internally and externally.

The treatment solution may also be poured inside the MDI components then drained to treat the internal component (e.g. the inner surface of a canister) only.

The treated canisters are preferably washed with solvent and dried at an elevated temperature for example 50-100°C optionally under vacuum.

In medical use the canisters in accordance with the invention contain a pharmaceutical aerosol formulation comprising a medicament and a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant.

Suitable propellants include, for example, C₁₋₄hydrogen-containing chlorofluorocarbons such as CH₂ClF, CClF₂CHClF, CF₃CHClF, CHF₂CClF₂, CHClFCHF₂, CF₃CH₂Cl and CClF₂CH₃; C₁₋₄hydrogen-containing fluorocarbons such as CHF₂CHF₂, CF₃CH₂F, CHF₂CH₃ and CF₃CHF₂CF₃; and perfluorocarbons such as CF₃CF₃ and CF₃CF₂CF₃.

5

Where mixtures of the fluorocarbons or hydrogen-containing chlorofluorocarbons are employed they may be mixtures of the above identified compounds or mixtures, preferably binary mixtures, with other fluorocarbons or hydrogen-containing chloro- fluorocarbons for example CHClF₂, CH₂F₂ and CF₃CH₃. Preferably a single fluorocarbon or hydrogen-containing chlorofluorocarbon is employed as the propellant. Particularly preferred as
10 propellants are C₁₋₄hydrogen-containing fluorocarbons such as 1,1,1,2-tetrafluoroethane(CF₃CH₂F) and 1,1,1,2,3,3,3-heptafluoro-n-propane (CF₃CHF₂CF₃) or mixtures thereof. 1,1,1,2-Tetrafluoroethane is of particular interest.

15 The pharmaceutical formulations for use in the canisters of the invention contain no components which provoke the degradation of stratospheric ozone. In particular the formulations are substantially free of chlorofluorocarbons such as CCl₃F, CCl₂F₂ and CF₃CCl₃.

20 The propellant may additionally contain a volatile adjuvant such as a saturated hydrocarbon for example propane, n-butane, isobutane, pentane and isopentane or a dialkyl ether for example dimethyl ether. In general, up to 50% w/w of the propellant may comprise a volatile hydrocarbon, for example 1 to 30% w/w. However, formulations which are free or substantially free of volatile adjuvants are preferred. In certain cases, it may be desirable to
25 include appropriate amounts of water, which can be advantageous in modifying the dielectric properties of the propellant.

A polar co-solvent such as C₂₋₆ aliphatic alcohols and polyols e.g. ethanol, isopropanol and propylene glycol, preferably ethanol, may be included in the drug formulation in the desired
30 amount to improve the dispersion of the formulation, either as the only excipient or in addition to other excipients such as surfactants. Suitably, the drug formulation may contain 0.01 to 5% w/w based on the propellant of a polar co-solvent e.g. ethanol, preferably 0.1 to 5% w/w e.g. about 0.1 to 1% w/w.

A surfactant may also be employed in the aerosol formulation. Examples of conventional surfactants are disclosed in EP 372 777. The amount of surfactant employed is desirable in the range 0.0001% to 50% weight to weight ratio relative to the medicament, in particular, 0.05 to 5% weight to weight ratio. Preferred surfactants are lecithin, oleic acid and sorbitan trioleate. Preferred formulations, however, are free or substantially free of surfactant.

Pharmaceutical formulations may contain 0.0001 to 50% w/w, preferably 0.001 to 20%, for example 0.001 to 1% of sugar relative to the total weight of the formulation. Generally the ratio of medicament to sugar falls within the range of 1:0.01 to 1:100 preferably 1:0.1 to 1:10. Typical sugars which may be used in the formulations include, for example, sucrose, lactose and dextrose, preferably lactose, and reducing sugars such as mannitol and sorbitol, and may be in micronised or milled form.

The final aerosol formulation desirably contains 0.005-10% w/w, preferably 0.005 to 5% w/w, especially 0.01 to 1.0% w/w, of medicament relative to the total weight of the formulation.

Medicaments which may be administered in aerosol formulations according to the invention include any drug useful in inhalation therapy and which may be presented in a form which is substantially completely insoluble in the selected propellant. Appropriate medicaments may thus be selected from, for example, analgesics, e.g. codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g. diltiazem; anti-allergics, e.g. cromoglycate (e.g. as sodium salt), ketotifen or nedocromil (e.g. as sodium salt); anti-infectives e.g. cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; anti-histamines, e.g. methapyrilene; anti-inflammatories, e.g. beclomethasone (e.g. as dipropionate), fluticasone (e.g. as propionate), flunisolide, budesonide, rofleponide, mometasone (e.g. as furoate), ciclesonide, triamcinolone (e.g. as acetonide) or 6 α , 9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carbo-thioic acid S-(2-oxo-tetrahydro-furan-3-yl) ester; anti-tussives, e.g. noscapine, bronchodilators, e.g. albuterol (e.g. as free base or as sulphate), salmeterol (e.g. as xinafoate), ephedrine, adrenaline, fenoterol (e.g. as hydrobromide), formoterol (e.g. as fumarate), isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol (e.g. as acetate), reproterol (e.g. as hydrochloride), rimiterol, terbutaline (e.g. as sulphate),

isoetharine, tulobuterol, 4-hydroxy-7-[2-[[2-[[3-(2-phenylethoxy)propyl]sulfonyl]ethyl]amino]-ethyl-2(3H)-benzothia-zolone; diuretics, e.g. amiloride; anti-cholinergics, e.g. ipratropium (e.g. as bromide), tiotropium, atropine or oxitropium; hormones, e.g., cortisone, hydrocortisone or prednisolone; xanthines, e.g. aminophylline, choline theophyllinate, lysine theophyllinate or theophylline. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts, (e.g. as alkali metal or amine salts or as acid addition salts) or as esters (e.g. lower alkyl esters) or as solvates (e.g., hydrates) to optimise the activity and/or stability of the medicament and/or to minimise the solubility of the medicament in the propellant. It will further be clear to a person skilled in the art that where appropriate, the medicaments may be used in the form of a pure isomer, for example, R-albuterol or RR-formoterol.

Particularly preferred medicaments for administration using aerosol formulations in accordance with the invention include anti-allergics, bronchodilators and anti-inflammatory steroids of use in the treatment of respiratory disorders such as asthma by inhalation therapy, for example cromoglycate (e.g. as the sodium salt), salbutamol (e.g. as the free base or the sulphate salt), salmeterol (e.g. as the xinafoate salt), formoterol (e.g. as the fumarate salt), terbutaline (e.g. as the sulphate salt), reproterol (e.g. as the hydrochloride salt), a beclomethasone ester (e.g. the dipropionate), a fluticasone ester (e.g. the propionate). Salmeterol, especially salmeterol xinafoate, salbutamol, fluticasone propionate, beclomethasone dipropionate and physiologically acceptable salts and solvates thereof are especially preferred.

It will be appreciated by those skilled in the art that the aerosol formulations according to the invention may, if desired, contain a combination of two or more active ingredients. Aerosol compositions containing two active ingredients are known for the treatment of respiratory disorders such as asthma, for example, formoterol and budesonide, salmeterol (e.g. as the xinafoate salt) and fluticasone (e.g. as the propionate ester), salbutamol and beclomethasone (as the dipropionate ester) are preferred.

A particularly preferred combination is a combination of fluticasone propionate and salmeterol, or a salt thereof (particularly the xinafoate salt).

Particularly preferred formulations for use in the canisters of the present invention comprise a medicament and a C₁₋₄ hydrofluoroalkane particularly 1,1,1,2-tetrafluoroethane and 1,1,1,2,3,3,3-n-heptafluoropropane or a mixture thereof as propellant, especially 1,1,1,2-tetrafluoroethane.

5

Preferred formulations are free or substantially free of formulation excipients. Thus, preferred formulations consist essentially of (or consist of) the medicament and the selected propellant.

10 Conventional bulk manufacturing methods and machinery well known to those skilled in the art of pharmaceutical aerosol manufacture may be employed for the preparation of large scale batches for the commercial production of filled canisters. Thus, for example, in one bulk manufacturing method a metering valve is crimped onto an aluminium can to form an empty canister. The particulate medicament is added to a charge vessel and liquefied
15 propellant is pressure filled through the charge vessel into a manufacturing vessel. The drug suspension is mixed before re-circulation to a filling machine and an aliquot of the drug suspension is then filled through the metering valve into the canister.

In an alternative process, an aliquot of the liquefied formulation is added to an open canister
20 under conditions which are sufficiently cold such that the formulation does not vaporise, and then a metering valve crimped onto the canister.

The cap may be secured onto the canister via welding such as ultrasonic welding or laser welding, screw fitting or crimping. Preferably the canister is fitted with a cap assembly,
25 wherein a formulation metering valve is situated in the cap, and said cap is crimped in place.

MDIs taught herein may be prepared by methods of the art (e.g., see Byron, above and WO96/32150) substituting conventional cans for those treated in accordance with the present invention.

30

Typically, in batches prepared for pharmaceutical use, each filled canister is check-weighed, coded with a batch number and packed into a tray for storage before release testing.

Each filled canister is conveniently fitted into a suitable channeling device prior to use to form a metered dose inhaler for administration of the medicament into the lungs or nasal cavity of a patient. Suitable channeling devices comprise for example a valve actuator and a cylindrical or cone-like passage through which medicament may be delivered from the filled canister via the metering valve to the nose or mouth of a patient e.g. a mouthpiece actuator. Metered dose inhalers are designed to deliver a fixed unit dosage of medicament per actuation or "puff", for example in the range of 10 to 5000 microgram medicament per puff.

Administration of medicament may be indicated for the treatment of mild, moderate or severe acute or chronic symptoms or for prophylactic treatment. It will be appreciated that the precise dose administered will depend on the age and condition of the patient, the particular particulate medicament used and the frequency of administration and will ultimately be at the discretion of the attendant physician. When combinations of medicaments are employed the dose of each component of the combination will in general be that employed for each component when used alone. Typically, administration may be one or more times, for example from 1 to 8 times per day, giving for example 1,2,3 or 4 puffs each time. Each valve actuation, for example, may deliver 5 μ g, 50 μ g, 100 μ g, 200 μ g or 250 μ g of a medicament. Typically, each filled canister for use in a metered dose inhaler contains 60, 100, 120 or 200 metered doses or puffs of medicament; the dosage of each medicament is either known or readily ascertainable by those skilled in the art.

A still further aspect of the present invention comprises a method of treating respiratory disorders such as, for example, asthma, which comprises administration by inhalation of an effective amount of an aerosol formulation as herein described from a metered dose inhaler of the present invention.

The invention will now be described further with reference to the following examples which serve to illustrate the invention but are not intended to be limiting:-

30 Example 1

Standard 12.5ml MDI canisters (Presspart Inc Cary NC) are immersed in a solution of 1% w/w compound of formula (I) in isopropyl alcohol for 12 hours at room temperature. The canisters are then drained and allowed to dry at 80°C under vacuum. The cans are then

purged of air and the valves crimped in place, and a suspension of about 31.8mg salbutamol sulphate in about 19.8g HFA 134a is filled through the valve.

Example 2

- 5 Example 1 is repeated except a suspension of about 4.25mg salmeterol xinafoate and about 8g HFA 134a is filled through the valve.

Example 3

- 10 Example 1 is repeated except a suspension of 22mg fluticasone propionate and 15g HFA 134a is filled through the valve.

Example 4

- 15 Example 1 is repeated except a suspension of about 44mg fluticasone propionate and about 12g HFA 134a is filled through the valve.

Example 5

Example 1 is repeated except a suspension of about 13.8mg fluticasone propionate with about 4mg salmeterol xinafoate and 8 g HFA 134a is filled through the valve.

20 Example 6

Example 1 is repeated except a suspension of about 29mg fluticasone propionate with about 21.4g HFA 227 is filled through the valve.

Example 7-12

- 25 Examples 1 to 6 are repeated except that a compound of formula (II) is employed instead of a compound of formula (I).

Examples 13-18

- 30 Examples 1 to 6 are repeated except that a silane derivative of perfluoropolyoxyalkane with a molecular weight in the range 1600-1750 is employed instead of a compound of formula (I).

It will be understood that the present disclosure is for the purpose of illustration only and the invention extends to modifications, variations and improvements thereto which will be within the ordinary skill of the person skilled in the art.

- 5 Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

Claims:-

1. A metered dose inhaler comprising an interfacial surface having a linear, non-cross-linked polymeric compound disposed thereon.
5
2. A component or accessory for use in a metered dose inhaler, comprising an interfacial surface having a linear, non-cross-linked polymeric compound disposed thereon.
3. A component or accessory as claimed in claim 2 selected from the group consisting
10 of a canister, a metering valve, a metering chamber, a channeling device and an actuator for use in a metered dose inhaler.
4. A metered dose inhaler as claimed in claim 1 or a component or accessory as claimed in claim 2 or claim 3 wherein the polymeric compound is disposed as a multi-
15 molecular layer thereon.
5. A metered dose inhaler as claimed in claim 1 or a component or accessory as claimed in claim 2 or claim 3 wherein the polymeric compound is disposed as a mono-molecular layer thereon.
20
6. A metered dose inhaler as claimed in any one of claims 1, 4 or 5 or a component or accessory as claimed in any one of claims 2 to 5, wherein the metered dose inhaler is suitable for consistently dispensing a dose of medicament ranging between 90 and 110% of a prescribed single dosage.
25
7. A metered dose inhaler as claimed in any one of claims 1, 4 to 6, or a component or accessory as claimed in any one of claims 2 to 6 wherein the polymeric compound is a fluorocarbon.
- 30 8. A metered dose inhaler, a component or accessory as claimed in claim 7 wherein the fluorocarbon is highly fluorinated

9. A metered dose inhaler as claimed in any one of claims 1 or 4 to 8, or a component or accessory as claimed in any one of claims 2 to 8, wherein the polymeric compound comprises a functional grouping which is capable of anchoring the compound to the surface thereof.

5

10. A metered dose inhaler, component or accessory as claimed in claim 9 wherein the compound is an organo-phosphate.

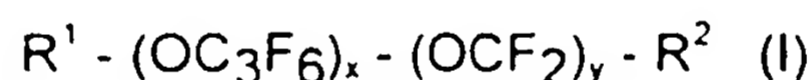
10

11. A metered dose inhaler, component or accessory as claimed in claim 10 wherein the compound is a phosphate based perfluoroether derivative.

12. A metered dose inhaler, component or accessory as claimed in claim 10 or claim 11 wherein the compound is a phosphoric ester.

15

13. A metered dose inhaler, component or accessory as claimed in claim 12 comprising an interfacial surface having a compound disposed thereon having the general formula (I):



20

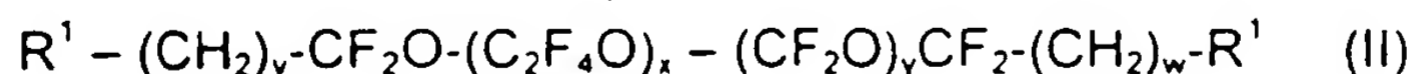
wherein R^1 comprises a fluoro-alkyl functional group;

x and y are such that the molecular weight of the compound is 350-1000; and

R^2 comprises a phosphoric ester functional group.

25

14. A metered dose inhaler, component or accessory as claimed in claim 12 comprising an interfacial surface having a compound disposed thereon having the general formula (II)



where R^1 comprises:

30

$-(OCH_2-CH_2)_z-OPO(OH)_2$ wherein x , y and z are such that the molecular weight of the compound is 900-2100 and v and w independently represent 1 or 2.

15. A metered dose inhaler, component or accessory as claimed in claim 14, wherein v and w are both 1.

16. A metered dose inhaler, component or accessory as claimed in claim 14, wherein v and w are both 2.

17. A metered dose inhaler, component or accessory as claimed in claim 9 wherein the compound is an organo-silane derivative.

18. A metered dose inhaler, component or accessory as claimed in claim 10 wherein the compound is a silane derivative of perfluoropolyoxyalkane.

19. A metered dose inhaler, component or accessory as claimed in claim 11 comprising an interfacial surface having a compound disposed thereon which is a silane derivative of perfluoropolyoxyalkane having a molecular weight in the range 1600-1750.

20. A metered dose inhaler as claimed in any one of claims 1 or 4 to 19, or a component or accessory as claimed in any one of claims 2 to 19, wherein the contact angle of the interfacial surface is greater than 70 degrees.

20

21. A metered dose inhaler as claimed in any one of claims 1, or 4 to 20, or a component or accessory as claimed in any one of claims 2 to 20, wherein the conductivity of the interfacial surface is greater than 2.4mS.

22. A metered dose inhaler, component or accessory as claimed in claim 21, wherein the interfacial surface is a metallic, metal alloy or plastics surface.

25

23. A metered dose inhaler, component or accessory as claimed in claim 22 wherein the interfacial surface is a metallic or metal alloy surface.

30

24. A metered dose inhaler as claimed in any one of claims 1, or 4 to 23, or a component or accessory as claimed in any one of claims 2 to 23, for storing and/or dispensing a medicament, wherein, during storage and/or dispensing, deposition of the

medicament on the metered dose inhaler, component or accessory is reduced by between 30% and 80%.

25. A component or accessory as claimed in any one of claims 2 to 24 which comprises
5 a canister containing a pharmaceutical aerosol formulation comprising a medicament, a fluorocarbon propellant and optionally a solvent.

26. A metered dose inhaler comprising a canister, and/or a metering valve, and/or a metering chamber, and/or a channeling device and/or an actuator as claimed in any one of
10 claims 2 to 25.

27. Use of a metered dose inhaler as claimed in any one of claims 1, 4 to 24 or 26, or a component or accessory as claimed in any one of claims 2 to 25, for dispensing a pharmaceutical aerosol formulation comprising a medicament and a fluorocarbon propellant.
15

28. Use as claimed in claim 27 wherein the pharmaceutical aerosol formulation to be dispensed is a medicament suspended in propellants selected from liquefied HFA 134a, 227 or a mixture thereof.

20 29. Use as claimed in claim 27 or 28 wherein the propellant is substantially free of adjuvants.

30. Use as claimed in any one of claims 27 to 29 in which the medicament is selected from fluticasone propionate, salbutamol, beclomethasone dipropionate, salmeterol,
25 pharmaceutically acceptable salts, solvates or esters thereof and mixtures thereof.

31. A process for obtaining a metered dose inhaler as claimed in any one of claims 1, 4 to 24 or 26, or a component or accessory for use in a metered dose inhaler as claimed in any one of claims 2 to 25, comprising the treatment of the interfacial surface with a linear,
30 non-cross-linked polymeric compound.

32. A process as claimed in claim 31 wherein the polymeric compound is disposed as a multi-molecular layer thereon.

33. A process as claimed in claim 31 wherein the polymeric compound is disposed as a mono-molecular layer thereon.

5 34. A process as claimed in any one of claims 31 to 33 wherein the linear polymeric compound is a fluorocarbon.

35. A process as claimed in claim 34 wherein the fluorocarbon is highly fluorinated.

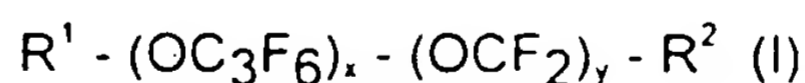
10 36. A process as claimed in any one of claims 31 to 35 wherein the polymeric compound comprises a functional grouping which is capable of anchoring the compound to the surface thereof.

15 37. A process as claimed in claim 36 wherein the compound is an organo-phosphate.

38. A process as claimed in claim 37 wherein the compound is a phosphate based perfluoroether derivative.

20 39. A process as claimed in claim 37 or 38 wherein the compound is a phosphoric ester.

40. A process as claimed in any one of claims 31 to 39, comprising the treatment of the interfacial surface with a compound having the general formula (I):



25

wherein R^1 comprises a fluoro-alkyl functional group;

x and y are such that the molecular weight of the compound is 350-1000; and

R^2 comprises a phosphate ester functional group.

30 41. A process as claimed in any one of claims 31 and 39, comprising the treatment of the interfacial surface with a compound having the general formula (II):



wherein R¹ comprises:

-(OCH₂-CH₂)_zOPO(OH)₂ wherein x, y and z are such that the molecular weight of the compound is 900-2100 and v and w independently represent 1 or 2.

5

42. A process as claimed in any one of claims 31 to 36 wherein the compound is an organo-silane derivative.

43. A process as claimed in claim 42 wherein the compound is a silane derivative of
10 perfluoropolyoxyalkane.

44. A process as claimed in any one of claims 31 and 36, 42 or 43 comprising the treatment of the interfacial surface with a compound which is a silane derivative of perfluoropolyoxyalkane having a molecular weight in the range 1600-1750.

THIS PAGE BLANK (USPTO)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
7 September 2001 (07.09.2001)

PCT

(10) International Publication Number
WO 01/64274 A3

(51) International Patent Classification: A61M 15/00,
C08G 65/00, C07F 9/09, C08L 27/16, B05D 5/08, B65D
83/14, C08F 8/18, G01N 1/24, C08K 3/00, C09D 127/12,
A61K 9/00, 9/16, A61M 35/00, C08G 65/32, 65/327,
65/336, C09D 171/00

(21) International Application Number: PCT/EP01/02213

(22) International Filing Date: 28 February 2001 (28.02.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0004794.4 1 March 2000 (01.03.2000) GB
0018674.2 28 July 2000 (28.07.2000) GB
0018684.1 28 July 2000 (28.07.2000) GB

(71) Applicant (for all designated States except US): **GLAXO
GROUP LIMITED** [GB/GB]; Glaxo Wellcome House,
Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB)

(72) Inventor: and

(75) Inventor/Applicant (for US only): **HAILEY, Mark, An-
drew** [GB/GB]; Glaxo Wellcome plc, Park Road, Ware,
Hertfordshire SG12 0DJ (GB).

(74) Agent: **CRAWLEY, Karen**; GlaxoSmithKline, Corporate
Intellectual Property, Two New Horizons Court, Brentford,
Middlesex TW8 9EP (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IL,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
with international search report

(88) Date of publication of the international search report:
7 February 2002

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: METERED DOSE INHALER

(57) Abstract: There is provided according to the invention a metered dose inhaler comprising an interfacial surface having a linear.

WO 01/64274 A3

INTERNATIONAL SEARCH REPORT

International Application No
PC1/EP 01/02213

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61M15/00 C08G65/00 C07F9/09 C08L27/16 B05D5/08
B65D83/14 C08F8/18 G01N1/24 C08K3/00 C09D127/12
A61K9/00 A61K9/16 A61M35/00 C08G65/32 C08G65/327

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61M C08G C07F C08L B05D B65D C08F G01N C08K C09D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
------------	--	----------------------

X	WO 96 32150 A (GLAXO WELLCOME INC ;ASHURST IAN C (US); HERMAN CRAIG S (US); LI LI) 17 October 1996 (1996-10-17) cited in the application	1,4-8
A	abstract page 2, line 8-11 page 2, line 15-20 page 3, line 4-9 page 7, line 4-28 page 8, line 10-15 claims 1,17,21,22	2,3,9-44

X	EP 0 687 533 A (AUSIMONT SPA) 20 December 1995 (1995-12-20) cited in the application	2-8
A	abstract; claim 8; examples page 2, line 40 -page 3, line 4 page 4, line 1 -page 5, line 42	1,9-44

-/-

☒ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex

* Special categories of cited documents *

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

Date of the actual completion of the international search

15 October 2001

Date of mailing of the international search report

22.10.01

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Lager, J

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/02213

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08G65/336 C09D171/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
------------	--	----------------------

X	EP 0 797 111 A (SONY CORP) 24 September 1997 (1997-09-24)	2-9,17, 18,42-44
A	abstract; claim 1; examples	1,10-16, 19-41

X	US 3 950 588 A (MCDUGAL JANICE E) 13 April 1976 (1976-04-13)	2-9,17, 18,42-44
A	the whole document	1,10-16, 19-41

X	EP 0 338 531 A (DAIKIN IND LTD) 25 October 1989 (1989-10-25)	2-12, 14-16
	cited in the application	
A	abstract	
	page 3, line 9,10; claims 1,2	1,13, 17-44

-/--

☒ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
 "Z" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

15 October 2001

22.10.01

Name and mailing address of the ISA

European Patent Office, P B 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Lager, J

INTERNATIONAL SEARCH REPORT

Int. Application No.

PCT/EP 01/03213

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where applicable of the relevant pages	Relevant to
X	WO 97 47000 A (SEAGATE TECHNOLOGY) 11 December 1997 (1997-12-11)	2-12, 14-16
A	abstract page 4, line 12-19 page 4, line 21 -page 12, line 32 ---	1,13, 17-44
A	EP 0 842 980 A (DYNEON LLC) 20 May 1998 (1998-05-20) abstract; claims 1,14-16 page 3, line 17-55 ---	1-44
A	EP 0 338 820 A (DOW CORNING) 25 October 1989 (1989-10-25) abstract page 2, line 3-15 page 3, line 8-13 ---	1-44
A	US 4 526 938 A (CHURCHILL JEFFREY R ET AL) 2 July 1985 (1985-07-02) abstract ---	1-44
A	US 4 961 966 A (STEVENS ROBERT K ET AL) 9 October 1990 (1990-10-09) abstract ---	
A	US 4 897 439 A (RAU STEVEN E ET AL) 30 January 1990 (1990-01-30) abstract -----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 01/02213

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,4-24,26-44

Claim 1 defines:

A metered dose inhaler comprising an interfacial surface having a linear, non-cross-linked polymeric compound disposed thereon.

2. Claims: 2-44

Claim 2 defines:

A component or accessory for use in a metered dose inhaler, comprising an interfacial surface having a linear, non-cross-linked polymeric compound disposed thereon.

INTEPATENTATIONAL SEARCH REPORT

Information on patent family members

Int. Patent Application No.

PC/EP 01/02213

Patent document used in search report	Publication date	Patent family members	Publication date
WO 9632150	A	17-10-1996	AU 718263 B2 13-04-2000
			AU 5481196 A 30-10-1996
			BG 102022 A 31-07-1998
			BR 9604977 A 09-06-1998
			CA 2217954 A1 17-10-1996
			CN 1186447 A 01-07-1998
			CZ 9703260 A3 18-02-1998
			EE 9700374 A 15-06-1998
			EP 0820323 A1 28-01-1998
			HU 9802391 A2 01-02-1999
			JP 11509434 T 24-08-1999
			NO 974736 A 11-12-1997
			NZ 306280 A 29-07-1999
			PL 322771 A1 16-02-1998
			SK 138997 A3 08-04-1998
			TR 9701169 T1 21-03-1998
			WO 9632150 A1 17-10-1996
			US 6143277 A 07-11-2000
EP 0687533	A	20-12-1995	IT 1269886 B 15-04-1997
			AT 196273 T 15-09-2000
			CA 2151577 A1 15-12-1995
			DE 69518798 D1 19-10-2000
			DE 69518798 T2 03-05-2001
			EP 0687533 A1 20-12-1995
			JP 8003516 A 09-01-1996
			US 5691000 A 25-11-1997
EP 0797111	A	24-09-1997	JP 9255919 A 30-09-1997
			EP 0797111 A2 24-09-1997
			US 5922787 A 13-07-1999
US 3950588	A	13-04-1976	NONE
EP 0338531	A	25-10-1989	JP 1268696 A 26-10-1989
			JP 1773056 C 14-07-1993
			JP 4060598 B 28-09-1992
			DE 68917189 D1 08-09-1994
			DE 68917189 T2 12-01-1995
			EP 0338531 A2 25-10-1989
			US 5132446 A 21-07-1992
WO 9747000	A	11-12-1997	US 5674169 A 23-02-1999
			CN 1231051 A 06-10-1999
			DE 19781801 T0 12-05-1999
			GB 2329643 A .B 31-03-1999
			HK 1018656 A1 22-12-2000
			JP 2000515902 T 28-11-2000
			WO 9747000 A1 11-12-1997
			US 6235689 B1 22-05-2001
EP 0642980	A	20-05-1998	EP 0642980 A2 20-05-1998
			CA 2098007 A1 12-07-1992
			DE 69226763 D1 01-10-1998
			DE 69226763 T2 08-04-1999
			EP 0566692 A1 27-10-1993
			JP 6504804 T 02-06-1994
			WO 9212199 A1 23-07-1992

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PL/EP 01,02213

Patent document cited in search report	Publication date	Patent family members:	Publication date
EP 0842980	A	US 5384374 A	24-01-1995
		US 5266650 A	30-11-1993
EP 0338820	A 25-10-1989	US 4951657 A	28-08-1990
		CA 1323148 A1	19-10-1993
		DE 68901805 D1	23-07-1992
		DE 68901805 T2	04-02-1993
		EP 0338820 A2	25-10-1989
		ES 2012717 A6	01-04-1990
		JP 1993213 C	22-11-1995
		JP 2009814 A	12-01-1990
		JP 7025667 B	22-03-1995
US 4526938	A 02-07-1985	AT 37983 T	15-11-1988
		AU 566010 B2	08-10-1987
		AU 1328083 A	27-10-1983
		CA 1246265 A1	06-12-1988
		DE 3378250 D1	24-11-1988
		DK 178583 A ,B,	23-10-1983
		EP 0092918 A2	02-11-1983
		ES 521713 D0	01-12-1984
		ES 8501779 A1	01-03-1985
		ES 535112 D0	01-12-1985
		ES 8602858 A1	16-03-1986
		FI 831368 A ,B,	23-10-1983
		GR 78529 A1	27-09-1984
		HU 198093 B	28-07-1989
		IE 54728 B1	17-01-1990
		IL 68426 A	31-08-1986
		JP 2090490 C	18-09-1996
		JP 4210928 A	03-08-1992
		JP 7088312 B	27-09-1995
		JP 1823155 C	10-02-1994
		JP 5017245 B	08-03-1993
		JP 58191714 A	09-11-1983
		NO 831413 A ,B	24-10-1983
		NO 841544 A	24-10-1983
		NO 164302 B	11-06-1990
		NZ 203970 A	11-04-1986
		PT 76576 A ,B	01-05-1983
		US 4942035 A	17-07-1990
		YU 89683 A1	30-04-1986
		ZA 8302601 A	29-02-1984
US 4961966	A 09-10-1990	US 4902318 A	20-02-1990
US 4897439	A 30-01-1990	AT 143991 T	15-10-1996
		AU 2300888 A	30-01-1989
		BR 8807598 A	29-05-1990
		CN 1030433 A ,E	18-01-1989
		DE 3855607 D1	14-11-1996
		DE 3855607 T2	06-03-1997
		EP 0366727 A1	09-05-1990
		IN 169990 A1	25-01-1992
		WO 8900175 A1	12-01-1989
		US 5536583 A	16-07-1996
		US 5093403 A	03-03-1992
		AT 103959 T	15-04-1994

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PC/EP 01/02213

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4897439	A	AU 605157 B2	10-01-1991
		AU 7496687 A	07-01-1988
		BR 8703650 A	22-03-1988
		CA 1309547 A1	27-10-1992
		CN 87105414 A ,B	02-03-1988
		DE 3789524 D1	11-05-1994
		DE 3789524 T2	13-10-1994
		EP 0252669 A2	13-01-1988
		IN 168335 A1	16-03-1991
		MX 166757 B	02-02-1993

THIS PAGE BLANK (USPTO)